REMARKS

This amendment is in response to the Final Official Action issued October 21, 2003 in connection with the above-identified application. A Request for Continued Examination is filed concurrently herewith. Claims 11 and 23 have been cancelled and the limitations of Claim 11 have been incorporated into Claim 1. Claim 1 has been amended to recite that the claimed method is a method of improving the pharmacokinetic profile of (2S,3S)-2-phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)methylamino-piperidine, or a pharmaceutically acceptable salt thereof. This amendment is supported by the specification as originally filed (page 1, lines 3-4) and therefore does not constitute new matter. Claim 1 is now pending in the application.

An Information Disclosure Statement and a PTO-AB-F820 form are enclosed.

Claims 1, 11 and 23 have been rejected under 35 U.S.C. 112, first paragraph, as allegedly not enabled. In particular, the Examiner has alleged that the invention as claimed in Claim 1 cannot be practiced without undue experimentation. *See* Official Action, page 3, last sentence.

In response, Claim 1 has been amended, without prejudice and in the interest of facilitating prosecution, to recite the limitations of now canceled Claim 11, *i.e.,* that the CYP2D6 Inhibitor is selected from the group consisting of quinidine, ajmalacine and pharmaceutically acceptable salts thereof. As acknowledged by the Examiner on page 2, line 17 – page 3, line 1, this combination is enabled by the Specification.

In view of the foregoing, withdrawal of the rejection of Claim 1 under 35 U.S.C. 112, first paragraph, as allegedly not enabled is respectfully requested.

Claims 1, 11 and 23 have been rejected under 35 U.S.C. 112, first paragraph, as allegedly obvious over Benet et al. (U.S. Patent No. 5,567,592) and Hess (WO 96/14845). In particular, the Examiner has alleged that Applicants in the specification have admitted that (2S,3S)-2-phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)methylamino-piperidine, quinidine, and ajmalacine are well-known CYP2D6 substrates (Official Action, page 4, lines 20-24), and has concluded that, in light of *In re Kerkhoven,* 205 USPQ 1069 (C.C.P.A. 1980), it would have been obvious to combine "two particular CYP2D6 substrates ... useful for the same purpose, i.e., mediating oxidative biotransformation for the major clearance mechanism in humans" (Official Action, page 5, lines 4-6) to obtain the present invention. The Examiner has further alleged that Benet et al. provide further motivation for the combination.

Applicants respectfully traverse. The combined use of (2S,3S)-2-phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)methylamino-piperidine with quinidine or ajmalacine is not obvious in view of Applicants' statements in the specification the cited art. In particular, Applicants' statements on page 4, lines 5-8 and 14-26 do not disclose or suggest that (2S,3S)-2-phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)methylamino-piperidine, quinidine, and ajmalacine are "useful for the same purpose," as stated by the Examiner and as required by *In re Kerkhoven.* As clearly recited

in the claims, the purpose of quinidine and ajmalacine is to inhibit CYP2D6, and not for "mediating oxidative biotransformation for the major clearance mechanism in humans" (Official Action, page 5, lines 4-6), as alleged by the Examiner. In contrast, (2S,3S)-2-phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)methylamino-piperidine is drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation, and therefore has a different purpose from quinidine and ajmalacine. Thus, the instant case is distinguishable from *In re Kerkhoeven*, and therefore *In re Kerkhoeven* is not applicable to this case.

Applicants also submit a Declaration under 37 C.F.R. 132 by the inventor, Ronald Scott Obach, together with the data enclosed. As stated in the Declaration, in the enclosed data, Tables 1-4 describe enzymatic kinetic parameters for the metabolism of (2S,3S)-2-phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)methylamino-piperidine (including O-demethylation and N-dealkylation) in various mammals, and Table 5 describes the inhibition of the same compound by Cytochrome P450 isoform specific inhibitors. In the figures, Figures 10 and 11 show a correlation between metabolism and inhibition of the same compound using inhibitors quinidine (Figure 10) and ketoconazole (Figure 11). The foregoing data and figures show a surprising effectiveness of (2S,3S)-2-phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)methylamino-piperidine in combination with a CYP2D6 inhibitor such as, for example, quinidine or ketoconazole, further supporting the non-obviousness of the invention over the cited art.

In view of the foregoing, withdrawal of the rejection of Claim 1 under 35 U.S.C. 103(a) as allegedly obvious over Benet et al. and Hess (WO 96/14845) is respectfully requested.

In view of the amendments and remarks made herein, applicants respectfully solicit the issuance of a notice of allowance. If a telephone interview is deemed to be helpful to expedite the prosecution of the subject application, the Examiner is invited to contact applicant's undersigned attorney at the telephone number provided.

The Commissioner is hereby authorized to charge any fees required under 37 C.F.R. §§1.16 and 1.17 or to credit any overpayment to Deposit Account No. 16-1445.

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